Synthetic Approach to *seco*-Tetracenomycin Natural Products Saccharothrixone A–C

Bhavani Shankar Chinta, Harikrishna Sanapa, Kamala Prasad Vasikarla, Beeraiah Baire

PII: S0040-4039(18)30488-X
DOI: https://doi.org/10.1016/j.tetlet.2018.04.031
Reference: TETL 49894

To appear in: *Tetrahedron Letters*

Received Date: 10 March 2018
Revised Date: 11 April 2018
Accepted Date: 12 April 2018

Please cite this article as: Shankar Chinta, B., Sanapa, H., Prasad Vasikarla, K., Baire, B., Synthetic Approach to *seco*-Tetracenomycin Natural Products Saccharothrixone A–C, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.04.031

Graphical Abstract

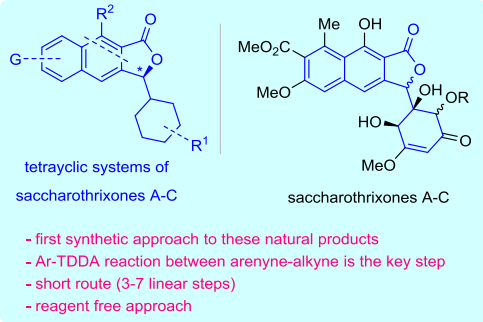
To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthetic Approach to *seco*-Tetracenomycin Natural Products Saccharothrixone A–C

Leave this area blank for abstract info.

Bhavani Shankar Chinta,[a] Sanapa,[b] Kamala Prasad Vasikarla[b] and Beeraiah Baire*

Department of Chemistry, Indian Institute of Technology Madras, Chennai-36, Tamilnadu, India.



This manuscript describes the first synthesis of tetracyclic framework of the novel *seco*-tetracenomycin natural products saccharothrixone A–C

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthetic Approach to *seco*-Tetracenomycin Natural Products Saccharothrixone A–C

Bhavani Shankar Chinta,[a] Harikrishna Sanapa,[b] Kamala Prasad Vasikarla[b] and Beeraiah Baire*[a]

Department of Chemistry, Indian Institute of Technology Madras, Chennai-600036, Tamilnadu, India.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Alkynes
Cycloadditions
Natural products
Phthalides
Total synthesis

ABSTRACT

Design and development of first synthetic approach to the functionalized tetracyclic framework of structurally novel seco-tetracenomycin natural products saccharothrixones A–C has been reported. A thermal dehydro Diels-Alder reaction of an arenyne-alkyne unit has been utilized as the key synthetic step. This strategy has been extended for the generation of a small library of diversely functionalized tetracyclic systems of seco-tetracenomycins. An approach for the synthesis of poly-hydroxyl tetracyclic system has also been described. This report represents the first synthetic approach to the tetracenomycin natural products saccharothrixones A–C.

The Aromatic polyketides are a class of natural products possessing a broad spectrum of bioactivities, such as antibacterial, antifungal, and anticancer. Recently, a screening program by Xiao et al., to identify potential aromatic polyketide-producing microorganisms led to the identification of the marine-derived actinomycete *Saccharothrix sp.*. Tetracenomycins (tcm) are a family of tetracyclic naphthacenequinones with a highly hydroxylated cyclohexenone moiety and significant antitumor activity.[1] The tetracenomycin X, an aromatic polyketide antibiotic, was identified as a major metabolite from the actinomycete *Saccharothrix sp.* 10-10. An extensive investigation of the secondary metabolite resulted in the isolation of three novel polyketide *seco*-tetracenomycins, saccharothrixones A–C, along with saccharothrixone D, which is a new tetracenomycin analogue possessing opposite configurations at all of the stereogenic centres. The saccharothrixones A–C represent first examples of *seco*-tetracenomycins where the quinone ring B is cleaved and re-formed into a furanone ring. These structures were elucidated by spectroscopic analyses and electronic circular dichroism calculations. Saccharothrixone D showed *in vitro* cytotoxic activity against the HepG2 cancer cell line with an IC_{50} value of 7.5 μM

[a] Department of Chemistry, Indian Institute of Technology Madras, Chennai-600036, INDIA
[b] Denisco Chemicals Pvt. Ltd. Hyderabad, INDIA
*Email: beeru@iitm.ac.in
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.xxxx/ejoc.2017xxxxx.

The structural novelty associated with the bioactivities attracted our attention. To the best of our knowledge so far, there are no reports appeared in the literature on the development of synthetic approaches to either for the synthesis of partial frameworks or for the total synthesis of these novle *seco*-tetracenomycin natural products (saccharothrixones A-C). Here in we report a first synthetic approach to this family of natural products. This strategy is rapid (3 steps) and diversity oriented to generate the functionalized derivatives of saccharothrixones A-C.

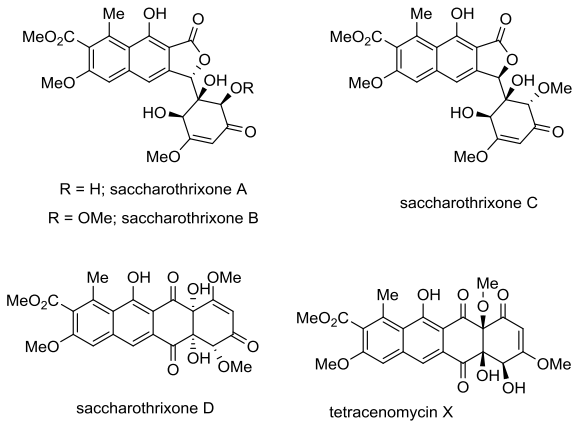
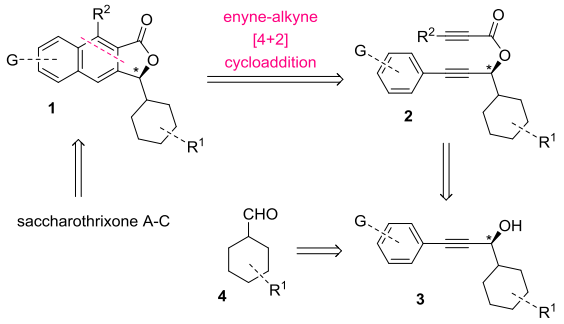


Figure 1. *seco*-Tetracenomycin natural products saccharothrixones A-C

We employed an arenyne-alkyne based dehydro Diels-alder reaction as the key step for the construction of the tetracyclic framework **1** of saccharothrixones A-C. According to our retro synthetic analysis (Scheme 1), the carbocylic system **1** of saccharothrixones A-C can be generated from the enyne-alkyne **2**

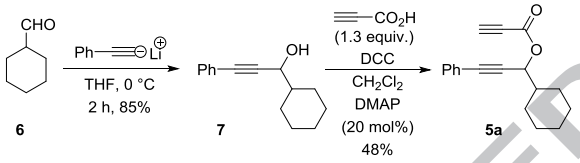
via an aromatic tetradehydro Diels-Alder (Ar-TDDA) reaction. This ester **2** can be obtained from the secondary propargylic alcohol **3** via DCC mediated esterification. The alcohol **3** can be efficiently prepared from cyclohexane-carbaldehyde **4**.



Scheme 1. Our retrosynthetic plan for the generation of carbocylic system of *seco*-tetracenomycin natural products saccharothrixones A-C

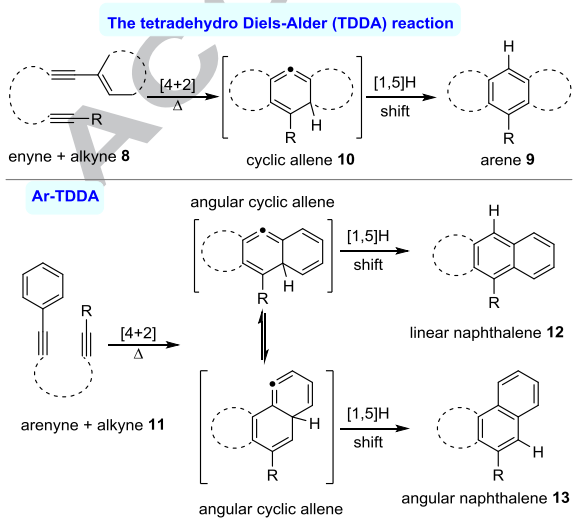
Results and Discussion

To understand the feasibility and ease of the proposed TDDA reaction, we performed a model study. Our synthetic approach begins with the preparation of the model substrate an arenyne-alkyne **5a**. Addition of the lithium phenylacetylide to the cyclohexane-carbaldehyde **6** at 0 °C in THF gave the secondary alcohol **7** in 85% yield after 2 h. The coupling of this alcohol **7** with the propiolic acid in presence of dicyclohexylcarbodiimide (DCC) and (4-dimethylamino)pyridine (DMAP) at 0 °C to RT afforded the arenyne-alkyne ester **5a** in moderate yield (48%).



Scheme 2. Synthesis of model arenyne-alkyne substrate for TDDA reaction

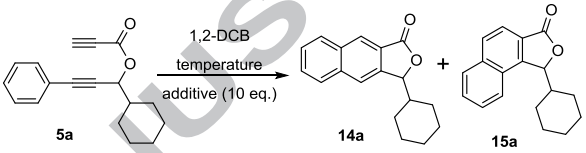
The tetradehydro Diels-Alder reaction (TDDA),[2] is a [4+2] cycloaddition[3] between an enyne (4π) and alkyne (2π) **8**, and would result in arene **9** *via* a [1,5]H shift of the initially formed cyclic allene intermediate **10** (Scheme 3). In case of arenyne-alkyne **11,** the Ar-TDDA reaction[4] would result in the formation of two isomeric products, linear and angular naphthalene derivatives **12** and **13**.



Scheme 3. The tetradehydro Diels-Alder (TDDA) and Ar-TDDA reactions

But, according to our design, the synthesis of carbocyclic framework, i.e., the linear naphthofuranone **1**, of saccharothrixones A-C involves an Ar-TDDA reaction. Therefore, initially, we performed an optimization study (Table 1) to find out a suitable reaction condition for the selective generation of linear naphthofuranone derivative **14a** from the arenyne-alkyne **5a**.

Accordingly, initially the arenyne-alkyne **5a** was heated as 1,2-dichlorobenzene solution at 110 °C (entry 1, Table 1). After 51 h, an inseparable (0.15:1) mixture of linear and angular furanone derivatives **14a** and **15a** was isolated in 73% combined yield. Next, performing the reaction in presence of phenol (10 equiv)[4b] at 110 °C (entry 2) resulted in the formation of the linear furanone **14a** as the exclusive product in 71% yield. Increasing the temperature to 130 °C (entry 3) resulted in the reduced reaction time (21 h) and gave the 70% of **14a**. Further increase of temperature to 150 °C (entry 4) gave both reduced reaction time (2 h) as well yield (58%) of the product **14a**.



entry	temp (°C)	time (h)	additive (eq.)	source	yield (%)	product
1	110	52	—	Δ	73	(0.15:1; **14a:15a**)
2	110	51	PhOH	Δ	71	**14a**
3	130	21	PhOH	Δ	70	**14a**
4	150	2	PhOH	Δ	58	**14a**

Table 1. Optimization study

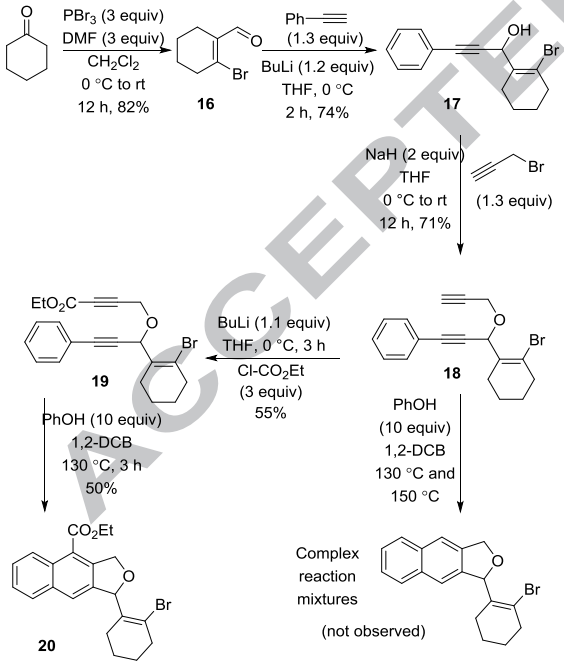
entry	enyne-alkyne	time (h), yield (%)	Product
1	**5b**	28 h, 57%	**14b**
2	**5c**	23 h, 64%	**14c**
3	**5d**	26 h, 56%	**14d**
4	**5e**	20 h, 60%	**14e**

reaction conditions: 5b-e, 1,2-dichlorobenzene, PhOH (10 eq.), 130 °C

Table 2. Synthesis of structurally divergent, functionalized tetracyclic systems of saccharothrixones A-C

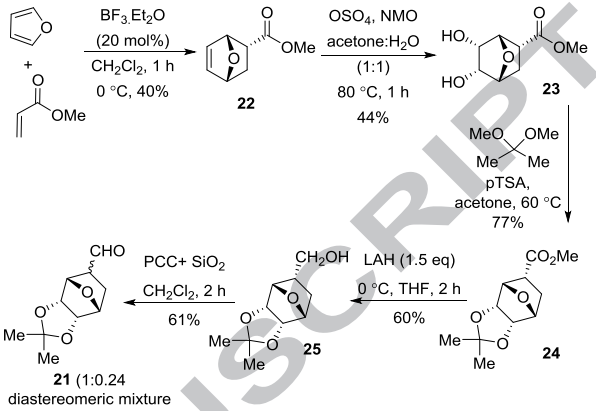
After finding an optimized condition (entry 3, Table 1) for the efficient formation of tricyclic lactones, we further extended this strategy to generate library of structurally divergent analogues frameworks (Table 2). Accordingly, various arenyne-alkynes **5b-e** have been employed under standard reaction conditions (1,2-DCB, PhOH (10 equiv) and 130 °C). All these substrates underwent smooth Ar-TDDA cyclization (20-28 h) to provide access to the corresponding linear naphthofuranone derivatives **14b-e** in moderate yields (56-64%). There was no detection of any traces of their angular counter parts.

Next, we aimed for functionalized cyclohexane bearing analogues of saccharothrixones A-C. Therefore, 2-bromocyclohexene-1-carbaldehyde **16** was chosen as the starting material.[5] Addition of phenylacetylide to the aldehyde **16** at ice cold temperature resulted in the formation of secondary alcohol **17**, in 74% yield. Initially, the reaction of alcohol **16** with propiolic acid in presence of DCC and DMAP failed to give any of the expected products. Instead it gave an unidentifiable product mixture after 3 h at 0 °C. So therefore, we planned to synthesize an analogous ether derivative **20**. Propargylation of the hydroxyl group present in **17** with NaH and propargyl bromide in THF at rt gave the bispropargylether **18** in 71% yield after 12 h. At this stage, heating the 1,2-DCB solution of arenyne-alkyne **18** at 130 °C as well as 150 °C, in presence of phenol resulted in the complex mixture of unidentifiable products. This may be due to the fact that the alkyne partner is inactivated. Disappointed by this outcome, we next prepared an activated arenyne-alkyne substrate **19** from **18**. Treatment of the **18** with ^{n}BuLi in THF at 0 °C followed by trapping the resultant acetylide by ethyl chloroformate gave the alkynoate **19** (55%). Upon subjection to standard reaction conditions, **19** gave the corresponding cyclised product **20** in moderate (50%) yield after 3 h.



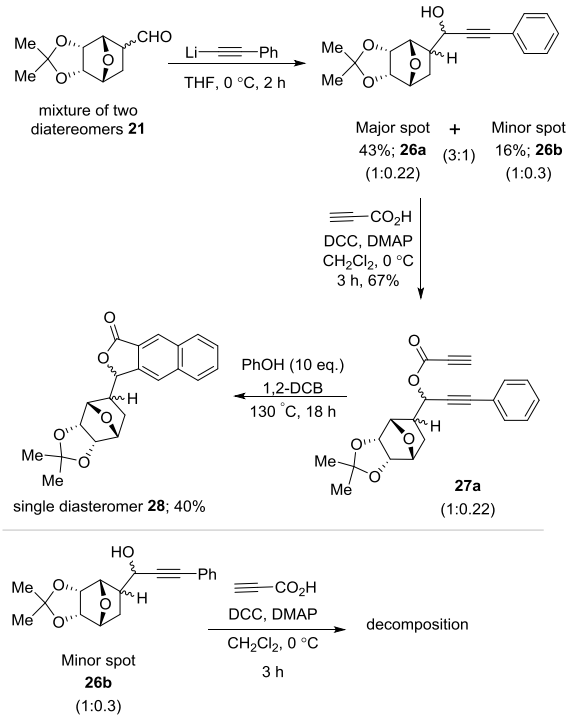
Scheme 4. Synthesis of functionalized linear isonaphthofuran

Subsequently, we focused on the synthesis of a poly-oxygenated, polychiral centred derivative of saccharothrixones A-C in its racemic form. Accordingly, our synthetic approach began with the preparation of the corresponding cyclohexane carbaldehyde **21** (Scheme 5). The Diels-Alder reaction between furan and methyl acrylate in presence of $BF_3.Et_2O$ at 0 °C gave the endo-ester **22** as the major in 40% yield.[6] Dihydroxylation of the olefin present in **22** with OsO_4 and NMO followed by the acetonide protection of the resultant vicinal diol **23** with 2,2-dimethoxypropane and pTSA at 60 °C afforded the ester **24** in excellent yield (77%).[7] Reduction of the ester group in **24** with $LiAlH_4$ followed by the oxidation of the resultant primary alcohol **25** with PCC-SiO_2 gave an inseperable (1:0.24) diastereomeric mixture of aldehydes **21**.



Scheme 5. Synthesis of poly-oxygenated cyclohexane-carbaldehyde **21**

We further proceeded with this mixture. Phenylacetylide addition to the aldehyde **21** at 0 °C gave a mixture of four diastereomeric seondary propargylic alcohols. To our delight, this time we could seperate two sets **26a** (major) and **26b** (minor), each containing two diastereomers (1:0.22) and (1:0.3) respectivley. Initially, The major mixture **26a** was taken further to complete the synthesis of respective tetracyclic framework. Coupling of the **26a** with propiolic acid in presence of DCC and DMAP in CH_2Cl_2 at 0 °C gave the corresponding ester **27a** (1:0.22) in 67% yield.



Scheme 6. Synthesis of poly-oxygenated tetracyclic isonaphthofuranone framework

Heating a solution of **27a** in 1,2-DCB and phenol at 130 °C for 18 h, underwent the anticipated Ar-TDDA cyclization to generate the linear naphthofuranone derivatives. To our surprise, a single diastereomeric linear naphthofuranone **28** was isolated as the

product in moderte yield (40%). We could not identify any traces of other diastereomeric cyclic product. The relative streochemistry of the isolated tetracyclic product **28** is not known. On the other hand, when we employed the another set of secondary propargylic alcohols **26b** in coupling with propiolic acid, the entire reaction mixture was decomposed to unidentifiable complex mixture.

In summary, we have developed a synthetic strategy for the first synthesis of functionalized tetracyclic frameworks of the natural products saccharothrixone A–C. We employed the aromatic tetradehydro Diels-Alder reaction between an arenyne and alkyne as the key step. We further extended this strategy for the generation of highly oxygenated tetracyclic framework of the natural products saccharothrixone A–C.

Acknowledgments

We thank We thank Department of Chemistry, IIT Madras for infrastructure facility. We acknowledge financial support from CSIR-INDIA (No.02(0209)/14/EMR-II) and Denisco Chemicals Pvt. Ltd. Hyderabad (RB/16-17/CHY/002/DENI/BEER). We thank Ms. Keerthana for helping BS for the characterizations of few compounds. BS thanks IIT Madras for HTRA fellowship.

Supplementary Material

Supplementary data (^{1}H, ^{13}C NMR spectra for all new synthesized compounds and experimental procedures) (PDF) associated with this article can be found in the online version, at http:// dx.doi.org/xxxxxxxxxx.

References and notes

1. M. Gan, B. Liu, Y. Tan, Q. Wang, H. Zhou, H. He, Y. Ping, Z. Yang, Y. Wang, C. Xiao, *J. Nat. Prod.*, **2015**, *78*, 2260.
2. (a) A. Michael, J. E. Bucher, *Chem. Zentrblt*., **1898**, 731; (b) P. Wessig, G. Müller *Chem. Rev*. **2008**, *108*, 2051; (c) R. L. Danheiser, A. E. Gould, R. F. Pradilla, A. L. Helgason, *J. Org. Chem.* **1994**, *59*, 5514; (d) J. R. Dunetz, R. L. Danheiser, *J. Am. Chem. Soc*. **2005**, *127*, 5776; (e) M. E. Hayes, H. Shinokubo, R. L. Danheiser, *Org. Lett.*, **2005**, *7*, 3917; (f) M. S. B. Wills, R. L. Danheiser, *J. Am. Chem. Soc*. **1998,** *120*, 9378; (g) B. S. Chinta, A. Siraswar, B. Baire, *Tetrahedron*, **2017**, *73*, 4178; (h) B. S. Chinta, B. Baire, *Eur. J. Org. Chem.*, **2017**, 3457; (i) B. S. Chinta, B. Baire, *Org. Biomol. Chem.*, **2017**, *15*, 5908; (j) B. S. Chinta, B. Baire, *Org. Biomol. Chem.*, **2018**, *16*, 262.
3. (a) S. Kobayashi, K. A. Jørgensen, Eds. Cycloaddition Reactions in Organic Synthesis; Wiley-VCH: Weinheim, **2002**; (b) J. A. Norton, *Chem. Rev*. **1942**, *31*, 319–523; (c) J. G.; Martin, R. K. Hill, *Chem. Rev*. **1961**, *61*, 537–562; (d) G. Brieger, J. N. Bennett, *Chem. Rev*. **1980**, *80*, 63; (e) H. B. Kagan, O. Riant, *Chem. Rev*. **1992**, *92*, 1007; (f) J. D. Winkler, *Chem. Rev*. **1996**, *96*, 167; (g) A. Kumar, *Chem. Rev*. **2001**, *101*, 1; (h) K. Takao, R. Munakata, K. Tadano, *Chem. Rev*. **2005**, *105*, 4779; (i) O. Diels, K. Alder, *Justus Liebigs Ann. Chem*. **1928**,*460*, 98.
4. (a) D. Rodrı´guez, A. Navarro-Va´zquez, L. Castedo, D. Domı´nguez, C. Saa´, *Org Lett.*, **2000**, *2*, 1497; (b) D. Rodrı´guez, A. Navarro-Va´zquez, L. Castedo, D. Domı´nguez, C. Saa´, *J. Am. Chem. Soc*. **2001,** *123*, 9178; (c) D. Rodrı´guez, A. Navarro-Va´zquez, L. Castedo, D. Domı´nguez, C. Saa´, *J. Org. Chem.* **2003**, *68*, 1938; (d) A. Ajaz, A. Z. Bradley, R. C. Burrell, W. H. H. Li, K. Daoust, J. L. B. Bovee, K. J. DiRico, R. P. Johnson, *J. Org. Chem.* **2011**, *76*, 9320; (e) B. S. Chinta, B. Baire, *Eur. J. Org. Chem.*, **2017**, 3381.
5. B. Salem, E. Delort, P. Klotz, J. Suffert, *Org. Lett.*, **2003**, *5*, 2307.
6. M. Kus, L. Artok, M. Aygun, *J. Org. Chem*, **2015**, *80*, 5494.
7. M. J. Moschitto, D. N. Vaccarello, C. A. Lewis, *Angew. Chem. Int. Ed.* **2015**, *54*, 2142.

Highlights of the manuscript:

1) *This report represents the first synthetic approach to the tetracenomycin natural products saccharothrixones A–C.*
2) Generation of a small library of diversely functionalized tetracyclic systems of seco-tetracenomycins
3) Mild and short synthetic approach for the frame work generation (4-5 steps)
4) A thermal dehydro Diels-Alder reaction of an arenyne-alkyne unit has been utilized as the key synthetic step.
5) An approach for the synthesis of poly-hydroxyl tetracyclic system has also been described